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SCHOOL OF AVIATION MEDICINE
RANDOLPH AIR FORCE BASE, TEXAS

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OBSERVATION OF LATENT EFFECTS FOLLOWING TOTAL-BODY GAMMA RADIATION IN THE BURRO

The results of continued observation of burro survivors of sublethal doses of total-body gamma-ray irradiation are reported. Five deaths occurred during the observation period of this project, 3.6 years from November 1954 to May 1958. In four decedents cause of death was associated with irradiation experience. The survivors seemed to make an early clinical and hematologic recovery and now appear to enjoy normal health and condition. Within two years after irradiation blood elements and weights were observed to be within values exhibited by nonirradiated controls.

This study began when the original investigators wished to retain a sizable group of female burros which had been exposed to gamma rays coincident to median lethality studies. Members of the Medical Advisory Group on Radiation Effects to the Surgeon General, USAF, deemed the retention worthwhile in order that a measure of possible latent effects could be observed in a large animal of relatively long life span. The Air Force has supplied the funds required for maintenance of the animals and for laboratory supplies.

The 49 burros receiving radiation are listed in table I according to dose group. The experimental animals were subjected to periodic examinations for a period of time after exposure to tantalum-182 and cobalt-60. They have been under daily observation since 1955. Hematologic samples are collected twice each year. On these occasions weights are recorded and eyes are examined. Bone marrow aspirations were performed through the 1957 mid-year examination. Detailed physical examination is made at any time an animal exhibits behavior or condition warranting it. A continuing search is made for meaningful methods with which to better evaluate the existence of latent radiation damage in the animals. Frank incidental illness in the experimental animal is treated in terms consistent with good practice. Prior to 1 March 1958 no prophylactic immunizations were routinely administered; however, since that time all animals have received tetanus toxoid as well as rabies vaccine. The decision to do this was based on the reasoning that naturally occurring infection with either tetanus or rabies would not constitute a meaningful challenge because of the mode of infection and the lack of uniformity in the population at risk.

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OBSERVATIONS

Survival

Five deaths in the experimental group have occurred since the project's inception. The survival time of decedents is shown in table II in relation to dose group. Animal 94, in the

TABLE I

Initial population of burros by exposure group

Burro group	Source	Number of burros	Date of exposure
D (321 r)	Ta^{182}	10	1 Sept. 1951
A (425 r)	"	9	"
E (545 r)	"	10	"
25 r/wk. (375 r)	Co^{60}	20	7 Dec. 1953
Control	—	10	—

TABLE II

Survival by group

Group	Dose (r)	Date of irradiation	Number surviving 15 May 58	Decedents (identification number)	Survival (years)	Remarks
D	321	1951	10/10			
A	425	1951	8/9	218	3	Thrombocytopenia
E	545	1951	8/10	232	4	Thrombocytopenia
				111	6.3	Ulcerative colitis Thrombocytopenic purpura
25 r/wk.	375	1954	18/20	7	3	Thrombocytopenic purpura
				94	4	Tetanus
Control		1951	10/10			

25 r/week group, died of tetanus with no clinical evidence of latent irradiation damage. It was possible to predict the deaths of three decedents as long as four months prior to occurrence; however, as in the case of animal III, group E, thrombocytopenia was undetected until the animal showed obvious signs of illness less than one month prior to death. With the exception of animal 169, group A, there are at the present time no indications of damage sufficient to predict fatalities within the near future.

Hematology

Burro groups D, A, and E, following the original single doses of radiation, experienced an early decrease in circulating leukocytes with a relatively greater decrease in lymphocytes. The magnitude of decrease by group was dose-related and reached a maximum of 19 percent of preirradiation values in group E during the second week postirradiation. Because of the different mode of irradiation, the blood response was different in animals of the 25 r/week group. In this group the weekly irradiations were discontinued at a total accumulated dose below the $LD_{0/30}$ from single irradiation exposure. At this time the circulating leukocytes were at 50 percent of preirradiation levels, with a relatively greater decrease in lymphocytes. A recovery process was evident in the circulating leukocytes three weeks after the weekly irradiations were discontinued. Numerical recovery of leukocytes was evident in all groups within two years after radiation exposure. At the present time leukocyte values for all irradiated groups are within the range of control averages. In figure 1 the trends in averages are shown. These data include serial counts from decedents.

Platelet counts were not routinely done on groups D, A, and E until some ten weeks after irradiation. The lowest recorded platelet averages were observed at eighteen weeks postirradiation. Recovery occurred over a two-year period. Reduction in platelets in the 25 r/week group was gradual and reached a maximum at approximately eight months following the first irradiation; recovery in platelet numbers occurred within the next eighteen months in most of the animals of this group. Figure 2 shows the serial change in platelets for all animals including decedents. These latter, without exception, sustained a loss in platelets either continuing from the time of irradiation or occurring shortly before death. Serial platelet and leukocyte counts for decedents and their respective groups are shown in figures 3, 4, and 5. One surviving animal, 169 of group A, has had a chronically low platelet count (average 50,000 per $mm.^3$, range 10,000 - 155,000)

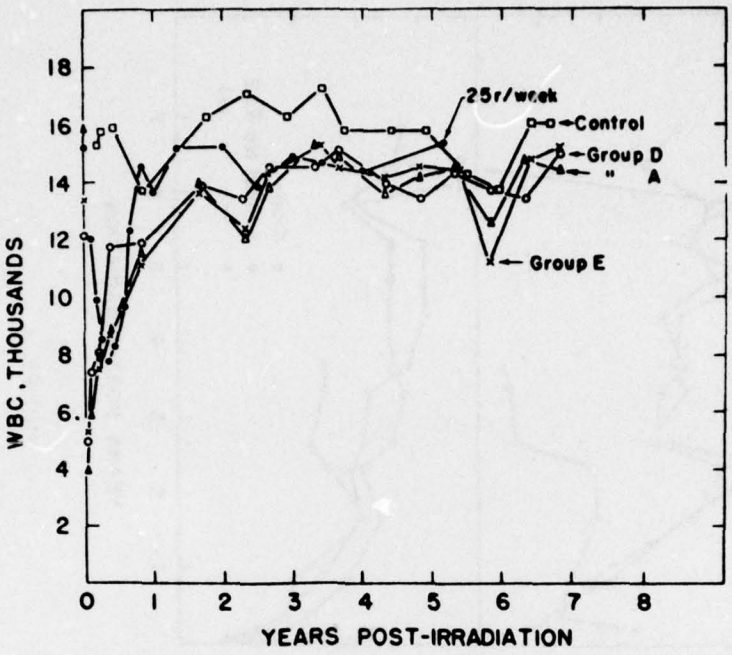

FIGURE 1

Serial leukocyte counts in survivor burros.

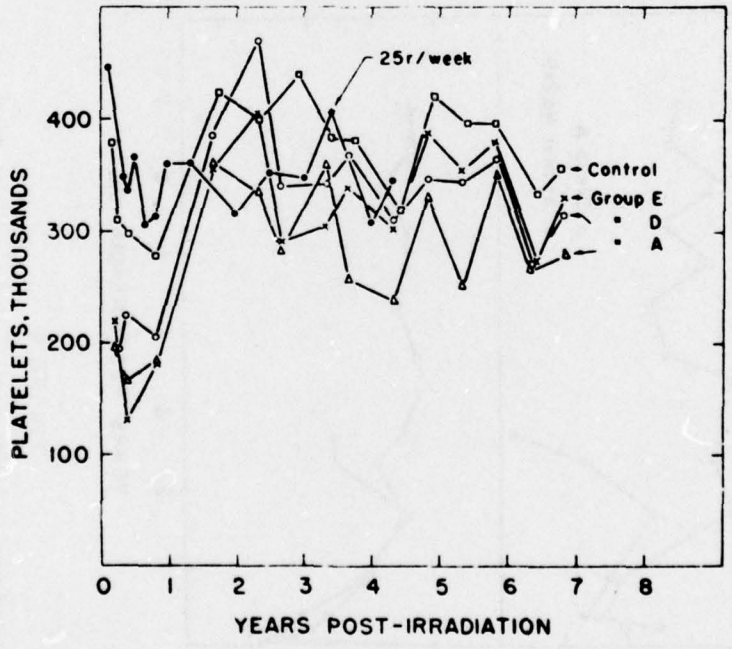

FIGURE 2

Serial platelet counts in survivor burros.

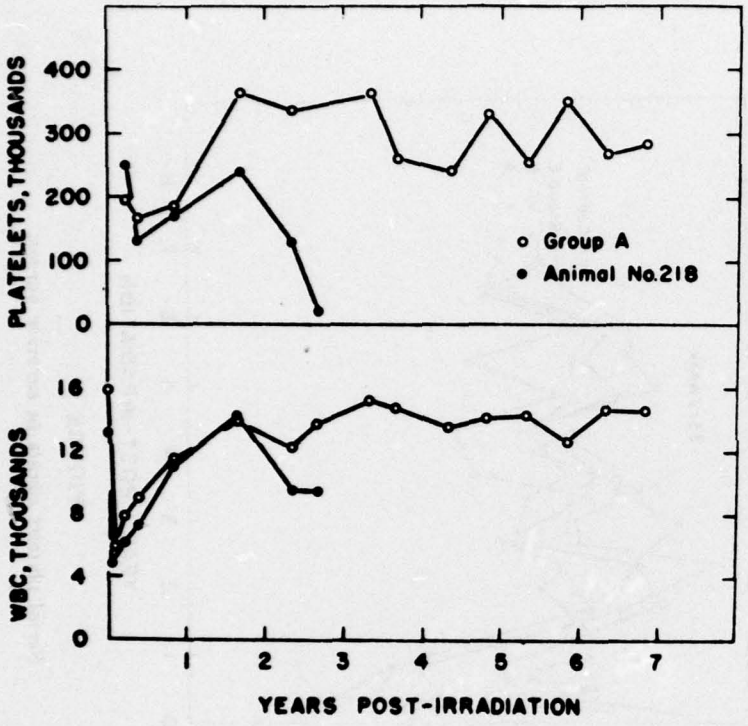

FIGURE 3

Platelet and total leukocyte counts in burro group A decedents.

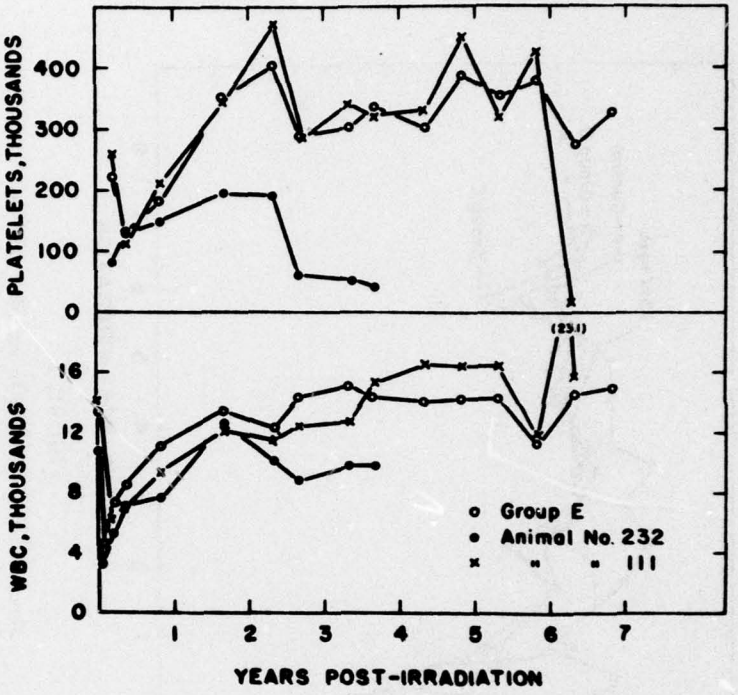

FIGURE 4

Platelet and total leukocyte counts in burro group E decedents.

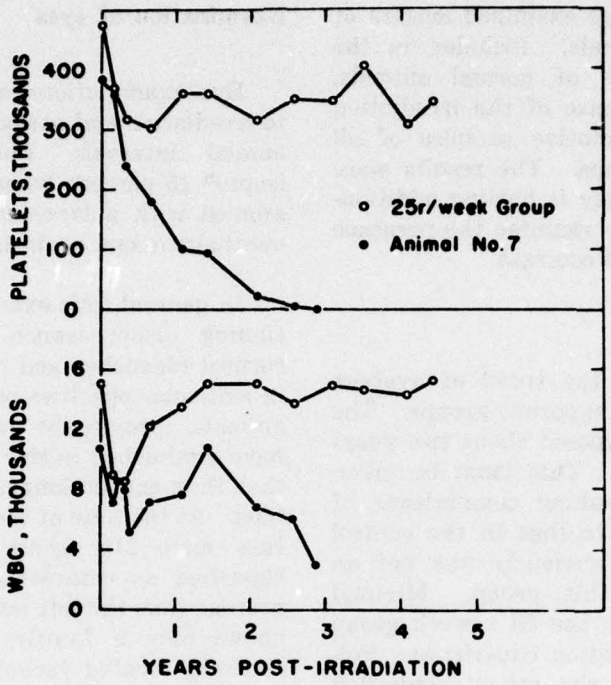

FIGURE 5

Platelet and total leukocyte counts in burro group 25 r/week decedents.

for the past three years. Her death has been predicted on the basis of this several times, but she remains in a general physical condition equal to that of others of her group.

Decrease in cellularity occurred in the red cell system in the single-dose groups. The limit of decrease and the recovery in hematocrit values were strikingly dose-dependent. In groups D and A this decrease was minimal, reaching lowest values during the third week postirradiation. The decrease of hematocrit values in group E was more definite with lowest values occurring also during the third week. In all three groups recovery to or above preirradiation levels was evident at ten weeks. For purposes of comparison, survivors of two other groups (F, 608 r; C, 690 r) showed continued decrease in hematocrit values beyond the third week followed by recovery to preirradiation values at three months. It is interesting to note that in two decedents, out of six in group C, which survived beyond the third week, one experienced a drop in hematocrit to 36 percent at 20 days, an increase to 40 percent at 67 days, and died of pneumonia and thrombocytopenia at 147 days. The other animal reached a recorded low in hematocrit at 16 percent at 34 days, a return to 18 percent at 67 days, and 23 percent at 125 days; this burro, exhibiting thrombocytopenia, died on the 146th day.

Hematocrit values showed no evidence of decreased cellularity in the erythropoietic system in the 25 r/week animals. At the present time hemoglobin and hematocrit values in all irradiation survivors are comparable to those in control animals.

In an effort to obtain additional methods of measuring physiologic change, especially any subtle change which could reflect the character of latent damage, a measure of leukocyte alkaline phosphatase (1, 2) was attempted during this report period. Dr. William Maloney,

Boston City Hospital, has examined smears of over one hundred animals. Included in the specimens were smears of normal animals, animals in the acute phase of the irradiation syndrome, and representative samples of all the burro survivor groups. The results were inconclusive. Dr. Maloney is holding additional smears with which to examine the presence of an as yet unidentified esterase.

Weights

Figure 6 illustrates the trend of average weights for the several exposure groups. The 25 r/week group was exposed about two years after the other groups. This must be taken into consideration in making comparisons of weight change relative to that in the control group; however, there obviously was not an early weight loss in this group. Minimal weight loss did occur in the 25 r/week group one year after the radiation experience. Following the pattern of the other irradiation groups normal growth-rate and weight gain began within two years postirradiation. During the past year body weight averages in all groups have fluctuated in a similar fashion.

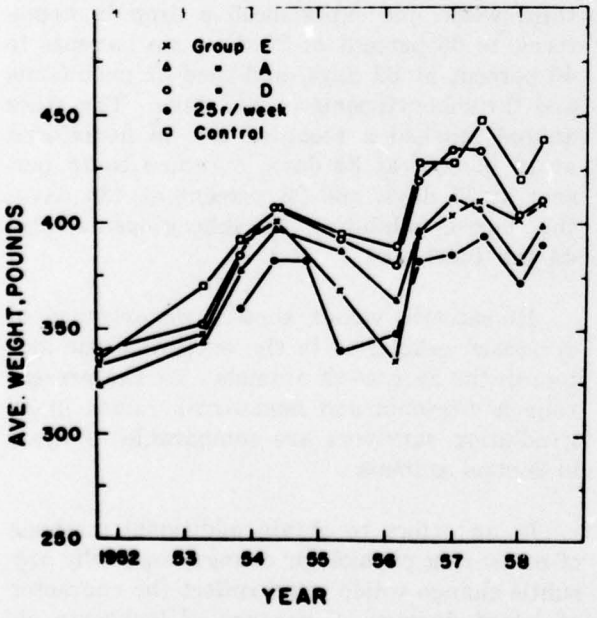

FIGURE 6

Average weights in survivor groups.

Examination of eyes

Eye examinations were accomplished prior to irradiation and periodically at approximately annual intervals. Following dilation with isopto^{R} (5 percent homatropine) eyes were examined with a translucent beam and with an ophthalmoscope again in January 1958.

In general, this examination revealed a continuing disappearance of previously marked corneal blemishes and opacities. Some change in lenticular opacities was evident also. In two animals, previously reported, lens opacities have diminished in size and quality to a degree that they can no longer be considered cataractous. At the time of the last reported examination burro 215, group D, exhibited opacities classified as cataract in both eyes. At the present time the left lens is clear, and the right shows only a faintly visible millet-seed-size, centrally located vacuole. Animal 138, also in group D, showed previously a distinct pattern of dotlike opacities on the anterior surface of the right lens; these are no longer visible. The distribution of lenticular opacities in the several groups is presented in table III. With the exception of finding what appears to be a progressive cataract formation in burro 52, group E, there is no significant increase in the size of previously reported cataracts.

The question of whether or not these eye changes are radiation-induced is unsettled. While it is clear that such changes do occur spontaneously, the preponderance of lesions have appeared in irradiated individuals.

Pathology

The first death in the burro band, occurring three years postirradiation, was that of animal 218 (group A) following the appearance of a marked thrombocytopenia (20,000 cells/mm.^{3}) of three months' duration. The cadaver exhibited gingival ulcers, leukoma, and blood droplets on the forehead, flanks, and legs. Animal 232, group E, succumbed four years after irradiation. The clinical history was similar to that of No. 218.

TABLE III

Distribution of lens opacities in survivor burros
(Numbers refer to identity of animal)

Group	Percent incidence*	Date		
		1956	1957	1958
D	26.7	214, 151	214, 151 215, 138	214, 151
A	0.0	None	None	None
E	4.0	None	None	52
25 r/wk.	15.8	33	33, 234 210, 80	33, 234 210, 80
Control	6.7	None	20	20

* Over-all incidence in irradiated animals is 13.6 percent.

Surviving irradiation by three years, the next animal to die was No. 7 of the 25 r/week group. This animal was observed and followed clinically throughout the last three months of her terminal illness. Death was associated with thrombocytopenic purpura.

Animal 111, group E, died 6.3 years following irradiation. The animal had been in apparent normal health until 26 December 1957 at which time, after several days of incessant rain, she appeared to be suffering from exposure. She was removed to dry quarters and treated for shock. At that time her body temperature was 99.4° F. with a pulse rate of 128 beats per minute. The blood picture showed hemoconcentration, granulocytosis, and lymphopenia. Platelets were low (40,000) but no outward sign of a bleeding tendency was noted until epistaxis was observed one day before death. The following day the animal fell from a standing position and died abruptly. Necropsy revealed a severe ulcerative colitis and massive hemorrhage from the lateral masses of the ethmoid and turbinates. Tissue sections and full necropsy report were forwarded to the Department of Radiobiology, School of Aviation Medicine, USAF. Histologic examination revealed evidence of hemorrhagic lymphatitis, focal edema in elastic arteries, and ulcerative colitis with possible glomerulitis.

One death due to tetanus occurred in animal 94, in the 25 r/week group. The animal exhibited classical signs of the disease on 28 February 1958 and survived an additional three weeks. Treatment was attempted but was of no avail.

Breeding program

In an effort to subject the survivor jennets to a normal stress of living, a breeding program was inaugurated during the report period. On showing signs of estrus, the animals were removed from pasture, confined, and bred over a period of three days or time sufficient to give a reasonable assurance of adequate coverage. Proven jacks were used as sires and rotated to allow for sufficient rest.

Although studies of the effect of irradiation on breeding efficiency were not included in the experimental design, we feel that the additional effort is justified for such indications as it may provide.

Thirty-eight animals were bred during the reported period. Of these, 16 animals are observed to be in foal. The distribution of pregnancies per number bred in each group is 5/6 in the nonirradiated control animals whereas 11/32 show pregnancy in the previously irradiated survivor groups.

The breeding program of the current season has been planned so that during the summer months, 30 June through 30 September 1959, all jennets will be bred in accordance with the estrus history and rebred if indicated upon

subsequent pregnancy examinations. The program includes complete recording of reproduction history of dams, and hematology and growth data of the newborn.

DISCUSSION

So far, routine general physical examination and blood sampling have been sufficient to prognosticate on the impending decline of a given animal subject. These measurements, together with the pathology examination, supply data on "What are the latent changes associated with irradiation damage" and "When do they occur?" By current methods it is possible to detect gross morphologic and functional changes either terminally or subterminally. In connection with life shortening, the desirability of developing methods capable of detecting subtle damage sooner and with greater sensitivity is obvious. In order to do justice to the material at hand, in the form of the irradiated large animal population, we plan to develop and employ new tests of animal capacity or general health status. Our first aim is to establish baseline data on the normal physiology of the burro and then to explore the possible difference between the normal and irradiated animals. We will make use of an additional survivor population from another project to increase the meaningfulness of this study.

SUMMARY

The present status of the survivor burro band is, with one exception of one animal, comparable to that of the control animals of the group. Five animals have died during the observation period covered by this report. In four decedents cause of death was associated with irradiation experience. Selected hematology and weight data are summarized for the more than six years following irradiation. The status of the breeding program is described.

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